Workshop on Development of New Technologies for Saliva and Other Oral Fluid-Based Diagnostics

Airlie House Conference Center, Virginia

September 12-14, 1999

National Institute of Dental and Craniofacial Research

National Institutes of Health

FOREWORD

Dear Colleagues:

We are experiencing a significant convergence and synthesis between the various health sciences, and the biological, chemical, physical and engineering sciences. In tandem, we are also experiencing profound changes in the demographics of our nation as well as in the patterns of disease from conception through senescence. Moreover, our mature and aging populations now have quality of life expectations that seek accelerated progress in health promotion, disease prevention, diagnostics including innovative imaging, treatment, therapeutics, and biomaterials.

In this remarkable environment, our Institute seeks to identify technologies that will enhance health promotion, disease prevention, and improve upon diagnostics, prognostics and therapeutics. One opportunity before us is to develop new technologies for saliva and other oral fluid-based diagnostics. A significant scientific literature is now available reflecting decades of progress towards understanding the cell, molecular and developmental biology of salivary glands as well as the constituents of saliva as a function of age, gender, health and disease. Proof of principle has been established for saliva to be used to monitor a number of systemic diseases and conditions, drug therapy for a number of clinical trials, and substance abuse such as alcohol consumption levels as reflected in oral fluids. Opportunistically, remarkable advances in miniaturization from nanotechnology, bioengineering technologies, and bioinformatics offer significant strategies to realize our shared goals. These and many other advances provide the rationale for this workshop.

The anticipated interactions and synergy between the scientific participants clearly demonstrate the value of cross-disciplinary and multidisciplinary approaches to solving complex problems.

Harold C. Slavkin, Director
National Institute of Dental and Craniofacial Research
National Institutes of Health

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Purpose and Goals

The National Institute of Dental and Craniofacial Research (NIDCR) wishes to seize the opportunity to capitalize on recent and future developments in the field of instrumentation research for oral-based diagnostics. The workshop is designed to:

- Examine the current status of saliva and other oral fluid-based diagnostics
- Identify the needs and opportunities for the development of technologies for saliva and other oral fluid-based diagnostics
- Provide a forum for biomedical researchers and instrumentation scientists to discuss the vision for solving current obstacles to technological progress for oral fluid-based diagnostics and
- Develop research recommendations to address opportunities for future investment by the NIDCR, including resource needs to enhance progress (i.e., national and/or regional resources, training, unique partnerships).

Workshop Program

Sunday, September 12, 1999

4:30 pm	**Registration**
6:30 pm	**Opening Remarks** Harold C. Slavkin, D.D.S. Director, National Institute of Dental and Craniofacial Research
7:00 pm	**Microfluidics for Biological Systems** George M. Whitesides, Ph.D.
7:45 pm	**Biosensors in Monitoring Disease: An Over View** Jerome S. Schulz, Ph.D.
8:15 pm	**Saliva and Other Fluids: Historic Perspective** Irvin D. Mandel, D.D.S.
8:45 pm	**Reception**

Monday , September 13, 1999

7:30 am	**Registration**
8:15 am	**Overview and Goals** Lawrence A. Tabak, D.D.S., Ph.D. Eleni Kousvelari, D.D.S., D.Sc.
8:30 am	**Nanofabrication for Biological Applications** Harold G. Graighead, Ph.D.
9:00 am	**Composition of Saliva and Other Oral Fluids** Frank G. Oppenheim, D.M.D., Ph.D. An update and Future Challenges

9:30 am	Physiology of Salivary Secretions: An Update and Future Challenges J. Ricardo Martinez, M.D, Ph.D.
10:00 am	**Break and Exhibits/Posters**
11:00 am	**Oral-Based Diagnostics: Successes and Failures** Daniel Malamud, Ph.D. Challenges for the Oral-Based Diagnostics
11:30 am	**Current State and Challenges of Diagnostic Technologies** Joseph Andrade, Ph.D.
12:00	**Lunch Break**
12:45 p.m.	**Sensor/Nanoinstrumentation: Can they Meet the Challenges of Oral-Based Diagnostics?** Marc J. Madou, Ph.D.
1:30 pm	**Break and Exhibits/Posters**

Working Groups:

There will be two concurrently working groups on Monday and on Tuesday. Each group will be asked to develop a 2-3 page summary of the discussions. The summary will contain a vision statement, 5-10 years goals for the field, a list of perceived impediments, possible solutions to achieving the goals, a short list of scientific priorities, and a brief implementation plan.

2:30-5:30 pm **Unique Aspects of Oral Fluids for Diagnostics (Group A and B)**

Discussions in each group will address questions such as:

- Is there sufficient information on normal values for constituents in saliva and other oral fluids?

- Which are the most informative metabolite (s) in oral fluids for diagnosing diseases (i.e., salivary molecules, cytokines, antigens, antibodies, electrolytes, steroids, drugs and their metabolites, nucleic acid, gases, various organisms, cells, enzymes, environmental pollutants, lipids, and fatty acids)?;

- Do saliva and other oral fluids offer information that cannot be obtained or obtained as readily or easily from other fluids, i.e., blood, urine?

- Do the measurements of oral fluid metabolites correlate with measurements of these metabolites in blood and/or urine?

- How the new technologies will improve understanding of saliva and other oral fluids in health and disease?

Unique Aspects of Oral Fluids for Diagnostics
(Group A)

Co-Moderators: Sylvia Daunert, Ph.D.
Paul Fidel Jr, Ph.D.

Participants: Ibtisam Al-Hashimi, B.D.S., Ph.D.
Richard Douglas
Lloyd G. Simonson, Ph.D., MBA
Philip C. Fox, DDS
Kenneth Gruber, Ph.D.
Amid I. Ismail, Ph.D.
Dushanka V. Kleinman, DDS, MScD
Steve Gutman, Ph.D
Eleni Kousvelari, DDS, D.Sc.
Harold G. Graighead, Ph.D.
Marc J. Madou, Ph.D.
Lawrence A. Tabak, DDS, Ph.D.
Richard George, Ph.D.
Keith Kardos, Ph.D.
Martha J. Somerman
Edward Rossomando, DDS, Ph.D., MS
Jerome S. Schultz, Ph.D.
J. Ricardo Martinez, MD, Ph.D.
Edith Schwartz, Ph.D.
Mary Bolton, Ph. D.

Unique Aspects of Oral Fluids for Diagnostics
(Group B)

Co-Moderators: Mira Engerton, DDS, Ph.D.
David R. Walt, Ph.D.

Participants Joseph Adrade, Ph.D.
Marilyn R. Carlson, DMD, MD, RAC

Darrell Chandler, Ph.D.
Louis DePaola, DDS, MS
William Giannobile, DDS, DMSc
David C. Duffy, Ph.D.
Charles Streckfus, DDS, MA
Leonard Tender
Debora Winn, Ph.D.
Charles Timchalk, Ph.D.
Gordon K. Jones, DDS, MS
James Lipton, DDS, Ph.D.
Daniel Malamud, Ph.D.
Irwin D. Mandel, DDS
Frank G. Oppenheim, DMD, Ph.D.
David Salzman, Ph.D.
Jonathan, A. Ship, DMD
Bernard Janicki, Ph.D.
Robert Betz, DDS

5:30 pm **Exhibits/Posters**

Tuesday, September 14, 1999

8:15 am **Introduction**
Irvin D. Mandel, DDS
Philip C. Fox, DDS

8:30 am **Public Health and Policy Issues**
Dushanka V. Kleinman, D.D.S., M.Sc.D.,
Deputy Director NIDCR,

Steve Gutman, Ph.D.
Division Director of Clinical Laboratory Devices, FDA

Barbara M. McGarey,
Senior Policy Advisor OTT/NIH

9:00 am **The Big Picture of Developing an Oral Fluid Diagnostic: The View of Industry**
David Parkinson, Ph.D.,
Vice President, Novartis Pharmaceuticals

Working Groups:

9:30-12:30 am **Use of New Technologies to Maximize the Use of Saliva and Other Oral Fluid in Diagnostics. (Groups C and D)**

Discussions in both groups will address topics such as:

- strategies and grand challenges in the development of new technologies (i.e., dry immunoassays, polymerase chain reaction, and microsensor technology) for rapid oral-based diagnostic assays in health and diseases
- the role of oral-based diagnostics in health care (i.e., in prevention, diagnosis and treatment of diseases)
- new developments in instrumentation and their application(s) for oral-based diagnostics
- what are the training needs for the health care practitioners to use these diagnostics?
- what are the regulatory issues related to the development and review of the new technologies?

Use of New Technologies to Maximize the Use of Saliva and Other Oral Fluid in Diagnostics. (Groups C)

Co-Moderators: Leonard M. Tender, Ph.D.
Louis DePaola, DMD, DMSc

Participants: Ibtisam Al-Hashimi, B.D.S., Ph.D.
Richard Douglas
Sylvia Daunert, Ph.D.
Paul Fidel Jr, Ph.D.
Lloyd G. Simonson, Ph.D., MBA
Philip C. Fox, DDS
Kenneth Gruber, Ph.D.
Amid I. Ismail, Ph.D.
Dushanka V. Kleinman, DDS, MS
Steve Gutman, Ph.D
Marc J. Madou, Ph.D.
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Harold G. Graighead, Ph.D.
Lawrence A. Tabak, DDS, Ph.D.
Richard George, Ph.D.
Keith Kardos, Ph.D.

	Martha J. Somerman, dds, Ph.D. Jerome S. Schultz, Ph.D. J. Ricardo Martinez, MD, Ph.D.
	Use of New Technologies to Maximize the Use of Saliva and Other Oral Fluid in Diagnostics. (Groups D)
Co-Moderators:	David C. Duffy, Ph.D William Giannobile, DMD, DMSc
Participants	Joseph Adrade, Ph.D. Marilyn R. Carlson, DMD, MD, RAC Darrell Chandler, Ph.D. David Parkinson, Ph.D. Edith R. Schwartz, Ph.D. Edward Rossomando, DDS, Ph.D., MS Mira Engerton, DDS, Ph.D. David R. Walt, Ph.D. Charles F. Streckfus, DDS, MA Debora Winn, Ph.D. Charles Timchalk, Ph.D. Gordon K. Jones, DDS, MS James Lipton, DDS, Ph.D. Daniel Malamud, Ph.D. Irwin D. Mandel, DDS Frank G. Oppenheim, DMD, Ph.D. David Salzman, Ph.D. Jonathan, A. Ship, DMD Robert Betz, DDS Bernard Janicki, Ph.D.
12:30-1:30 pm	**Lunch and Exhibits/Posters**
1:30 pm	**Reporting of the Working Groups** Larry A. Tabak, Moderator
3:30 pm	**Adjourn**

Workshop Report

Executive Summary

The purpose of the workshop: "Development of New Technologies for Saliva and Other Oral Fluid-Based Diagnostics convened by the NIDCR was to identify needs and opportunities for developing technologies for oral fluid based-diagnostics, and to develop recommendations that will serve as underpinnings for future investment by the Institute. The workshop participants, represented academia, industry, regulatory agencies, national research laboratories. The workshop's structure ensured that the recommendations would address priorities among a wide range of biological, chemical and engineering sciences, and that would involve multidisciplinary teams of scientists working in public and private institutions. Implementation of the recommendations will realize the goal of bringing innovative concepts and approaches to the development of new technologies for oral fluid-based diagnostics in health and disease.

The enthusiasm and excitement generated by the workshop participants are important indicators of the interest and opportunities in the area of oral based-diagnostic technologies.

Boundaries are disappearing between the life and the physical science. The interactions and creativity of interdisciplinary teams are contributing to a new understanding of basic mechanisms and to the development of novel products and innovative technologies. Plenary speakers posed provocative questions that were considered by the working groups. A summary of the presentations and the conclusions of the working groups are included in the full report. The primary scientific priorities and implementation strategies follow:

Scientific Priorities

1. Develop and utilize new technologies for *in vitro* and *in vivo* monitoring of oral components related to oral and systemic disease as well as of a salivary "fingerprint" profile. To achieve that there is a need to identify diagnostic markers for systemic and oral disease (e.g., biomarkers for cardiovascular disease and cancer as well as biomarkers for periodontal disease and dental caries); and for drug monitoring (drug compliance, drug abuse, pharmacokinetics, and pharmacogenomics). The utilization of emerging technologies such as micro- and nano-fabrication, miniaturized analytical systems, microfluidics, microsensors, and high density arrays of DNA will facilitate analysis of oral fluid-derived components (cells, DNA/RNA, proteins, hormones, drugs, metabolic products).

2. Facilitate the alignment of technology with basic science and with application. Exciting new oral-based diagnostic technologies can be envisioned arising from advances in basic science and engineering. Their fruition in clinical practice depends on effective translational research and dissemination into general use. The design and research of oral fluid-based diagnostics is poised to contribute to population studies, clinical trials, databases, regulatory science,

products and services that will facilitate new prevention and therapeutic strategies to meet both today's and tomorrow's patient needs.

3. Catalyze the vitality of multidisciplinary teams that will be instrumental in synthesizing and integrating information from diverse fields into focused application-oriented solutions.

Implementation Strategies

1. Establish new interdisciplinary/collaborative programs combining dental, medical, biological, chemical and engineering science approaches to create innovative technologies such as microfluidics, separations, recognition chemistry, and computer engineering for oral fluid-based diagnostics. Foster academic-industry partnerships and broader interactions with government laboratories.

2. Increase emphasis on training of a new breed of individuals with expertise that can facilitate collaborations among disciplines (single or multi-institution-based) (graduate students, postdocs, and clinical fellows).

3. Increase “customer” and general public input (clinicians, ER physicians, dental professionals and diagnostic industry).

4. Provide continuing education to the dental and other health professionals in the advantages, indications and usage of oral-based testing. There is also a need to provide education/information to other health professions and interested groups about the advantages and indications and usage of oral- based testing. Foster communication between dental and sensor/biosensor communities for near future development and utilization of clinically significant diagnostics.

5. Establish communication strategies for an on-going dialogue among academia, industry, government (i.e., FDA) and the public. For example, facilitate the communication by creating accessible, user-friendly databases of molecular, clinical, physio-chemical, and engineering knowledge and integrative principles.

Summary of Working Groups Report

Unique Aspects of Oral Fluids For Diagnostics (Group A)

Co-Moderators: Paul Fidel, Jr. , PhD and Sylvia Daunert, PhD.

Vision Statement

A global approach bringing together basic scientists, clinicians, and engineers would be most feasible to address the issue of oral fluid diagnostics. Such an approach will centered on identifying a saliva or oral fluid "fingerprint". For this, engineers would develop strategies to analyze whole saliva or oral fluids by microtechnologies and identify a pattern "fingerprint". Such an approach could be used across several disciplines (i.e., basic science, infectious disease, oral disease, diagnostics) to answer specific questions and have the potential to develop into a multi-billion dollar industry.

Scientific Priorities (5-10 yr goals)

1. Salivary 'fingerprint' profiles to correlate to many clinical conditions such as risk factors, susceptibility to infection/disease, general health status

2. Immediate implementation using current microtechnologies such as proteome (soluble fraction), genome (cellular fraction)

3. Obtain large amounts of information regarding several analytes using single technique.

4. Overcome the problems of dealing with specific analytes by establishing normal values of specific analytes, correlating specific analytes to clinical condition and correlating oral fluid constituent to plasma.

Barriers and Solutions

Barrier: Sensitivity, selectivity, sample processing, storage and retrieval, and technology that integrates microsensing, array, and high throughput detection. *Solution:* Gather more information from the basic scientists and clinicians (i.e., model target analytes, capture analytes, etc.) to provide engineers and analytical chemistry scientists with knowledge on oral fluids.

Barrier: There is not a fingerprint of oral fluid components/constituents. *Solution:* A global approach may be a viable alternative to conventional approaches, recognizing the struggles basic scientists have endured over the past several decades. Although broad in scope, it was felt that the use of a more global approach together with microengineering (i.e., microfluidic) is needed. Appropriate technologies would move the field of oral-based diagnostics to the next level. This

includes addressing both basic science issues as well as the needs of the commercial oral diagnostic industry.

Barrier: Correlation of substances between saliva and plasma. *Solution:* A correlation to a clinical condition could be achieved. If so, a correlation between the target substance in the two fluids is not required.

Barrier: Localized detection of analytes. *Solution:* Design and development of microsensors capable of small volume detection in spatially defined regions.

Barrier: Caution was raised for employing the "global fingerprint" approach for clinical purposes since the fingerprint would not include a specific clinical analyte and the sample variability may preclude interpretation. *Solution:* Microfluidic technologies could be implemented/developed for a " fingerprint" now as opposed to sometime in the future for a wide variety of clinical conditions.

Barrier: Individual variability of oral fluid components. *Solution*: Uniform method of sampling, bioinformatics/biostatistics.

Barrier: Resolution of fingerprint components. *Solution:* Engineering design and improved detection, reagents, and instrumentation.

Barrier: Difficulty in communication and integration (engineering, clinical, and analytical communities). *Solution:* Explore successful models for multidisciplinary programs for research and training.

Implementation Strategies:

1. The NIDCR should use a multidisciplinary approach to oral fluid detection using microtechnologies (i.e., basic scientists and engineers working together towards a common goal). The R21 (Exploratory/Developmental Grant) and integrated R01s and/or similar funding mechanisms can be used to allow multidisciplinary/multi-investigator approach with direct cost restrictions large enough to support the mechanism.
2. Emphasis should be placed on educating a new breed of scientists with expertise among disciplines through training programs (single or multi-institution-based) (graduate students, postdocs, and clinical fellows) involving basic scientists and engineers/anaytical chemists. Also “customer” (clinicians, ER physicians, dental professionals and diagnostic industry) and general public input should be encouraged.
3. The NIDCR should foster the development of new technologies such as microfluidics, separations, recognition chemistry (alternative/improved binding, motion vs. binding), in vivo detection/microsensors as well as adoption of bioinformatics (computer engineering).

Unique Aspects of Oral Fluids for Diagnostics (Group B)

Co-Moderators: Mira Edgerton, DDS, PhD and David R. Walt, PhD

Vision Statement

Increase understanding of the function of salivary molecules and the role that they play in health and disease are essential to developing accurate salivary diagnostic tests. Further characterization of the basic functions and interrelationships of salivary components is essential. This will permit application of our knowledge to diagnosis and evaluation of clinical treatment outcomes. Emphasis should be placed on areas where superiority of saliva over other fluids such as blood or urine as a diagnostic tool is apparent. Several salivary analytes were identified which have the potential to provide unique diagnostic information of systemic disease: sterol hormones, antibody levels (HIV), environmental toxins (mercury), therapeutic or recreational drug levels. These tests could be of high value in undeveloped countries (where clean needles are less available) or homeless populations. High density sensor technology may be used to collect requisite information in identifying oral diseases or alterations in host defense systems in the mouth that are multifactoral in origin by providing simultaneous genomic and proteomic information.

Goals for the Next 5-10 Years

- Comprehensively relate and define salivary molecules and their function in relationship with health, disease and in response to medications and risk behaviors.

- Design smarter sensors to detect functions (e.g. infection, toxicity, breach of host defense) rather than specific analytes (anticipatory). Teach sensors to discriminate encounters (bad or good), make correlations between molecules or conditions that resemble each other.

- Establish more complete quantitative and qualitative values for salivary molecules that participate in oral defense mechanisms in health and disease.

- Develop oral diagnostic tests of systemic disease such as: herpes, osteoporosis, hepatitis C, tuberculosis, STD (antigens for gonococci, chlamydia,), compromised organ function (pulmonary, kidney, liver), or autoimmune disorders. Ideally these tests will provide rapid diagnostic information so that it could be used in hospital emergency rooms or other situations requiring immediate information.

- Use microfluidics to study rheology and lubrication functions of saliva as well as potential heterotypic complex formation.

- Evaluate the suitability of using saliva for diagnostic biomarkers of rare events and to determine heterogeneity across populations.

- Develop technologies which use saliva as a temporal biomonitor. These may involve development of laboratory or home based diagnostic systems to evaluate individual patients and or populations at risk by genomic, proteomic and metabolic diagnostic systems.

- Emphasize predictive and preventive medicine through molecular diagnostics (gene expression analysis, etc) since saliva is the fluid of choice for DNA analysis (DNA from saliva is very pure).

- Develop and refine approaches for monitoring ongoing drug metabolism and/or systemic drug levels using oral biomonitors (understanding of oral drug levels in relationship to metabolism) as well as compliance with drug regimens.

- Understand the distribution of salivary components and host defense mechanisms within a population or across populations (diabetics, postmenopausal women, etc.) and determine their relationship with disease, health status and at risk behaviors (smoking, etc.). Diagnostic tests of those individuals at risk may be predicted from sensor arrays that could be office (DDS/DMD/MD) based.

- Develop new saliva-based biomarkers of periodontal diseases, which more accurately reflect current disease status such as biochemical markers of bone loss.

- Continue and expand efforts to use salivary glands to treat local and systemic diseases.

- Determine whether salivary molecules, particularly antimicrobial molecules, continue to retain function or acquire other functions as they pass further into the GI system.

- Investigate the role of healing factors and growth factors in saliva and determine their contribution to wound healing or regeneration.

Barriers and Solutions

Barrier: Cost of development is a serious issue. *Solution:* NIH support for fostering collaboration among different institutes and centers as well as involvement of the Department of Energy, DARPA, NSF, NIST, industry and others.

Barrier: Users of salivary diagnostic testing (pathologists, clinical chemists, etc.) have concerns about possible changes in laboratory testing. Medical records is another issue. *Solution:* Increase awareness of the potential of oral based diagnostics and increase input from internists as to what is important for them in a salivary test.
Barrier: Industry will not begin developing oral based diagnostics without market assurance. From commercial side, there must be a market. It is not clear who will pay for it? *Solution:*

Involvement of small companies since some of the markets are not large. Better correlation of treatment outcomes to diagnostic tests. For example, demonstrate that a test is necessary for appropriate treatment of a particular disease. Educate physicians, hospital administrators, etc. about the tests. Everything has to be easy and routine.

Recommended Priorities

1. Further support basic research in salivary protein functional studies with the goal of identifying "best" candidates for use in diagnostic technologies for identifying oral diseases or identifying populations at risk for these diseases.

2. Initiate research on oral diagnostic systems for identification of valid biomarkers of systemic disease or infections such as carcinomas (breast, prostrate, lung), metabolic diseases (diabetes, altered kidney or liver function) or infectious diseases (tuberculosis, rubella, sexually transmitted diseases).

3. Align technology with basic science and with application. Input from internists is required as to what is important for them in a salivary test. Use analytical technologies (i.e., MALDI-TOF, Capillary electrophoresis) that could solve a number of important saliva characterization problems. Acquaint one community with techniques of another community.

Implementation Strategies

Increase support of these research initiatives through dedicated funding mechanism (RFA) that encourage multidisciplinary collaboration and partnerships among academia, industry and other agencies.

Use of New Technologies to Maximize the Use of Saliva and Other Fluids (Group C)

Co-Moderators: Leonard M. Tender, PhD and Louis G. DePaola, DDS, MS

Vision Statement

There is consensus that oral fluids provide worthwhile routes for assessment of systemic health and disease states, and exposure to environmental, occupational, and abusive substances. Indeed oral fluid based diagnostics may in many instances prove more accessible, accurate, less expensive, and present less risk than current methodology. In addition, application of established and emerging technologies for oral fluid analysis may provide worthwhile insights into oral health and disease.
Clearly a multidisciplinary approach encompassing scientists, clinicians and engineers will most effectively maximize the diagnostic and research value of oral fluids.

Goals for the Next 5-10 Years

- Identification of oral fluid components detectable by current technologies that are markers of highly prevalent systematic disease for which rapid sensitive, and inexpensive diagnosis would highly impact patient treatment and/or reduce care giver risk.

- Identification of additional oral fluid components that are markers for periodontal, oral, and systemic health, organ function, occupational or environmental contamination, and substance abuse.

- Development and transition of current diagnostic technologies for detection of oral fluid derived markers.

- Development of technologies for simultaneous multi-analyte detection. Such technologies are to allow simultaneous assessment of multiple conditions of health and disease and to uniquely characterize individuals with respect to susceptibility to adverse pharmacological interactions. These technologies are also to allow elucidation of simultaneous activity of multiple analytes in response to a single condition for which analysis of a single analyte is less insightful or less accurate. Technologies to be developed include (but not limited to) microfluidics, sample preparation and treatment, sensor arrays, and transduction methods). Miniaturization is essential for such multiple analyte analysis of oral fluids

- Develop diagnostic codes for oral fluid-based tests.

Implementation Strategies

- Foster communication between clinical, science, and engineering communities for near future development and utilization of clinically significant diagnostics.

- Develop educational programs with curriculum in both dental science and biotechnology.

- Provide continuing education to the dental community in the advantages indications and usage of oral based testing.

- Provide education/information to other health professions for interested groups (corrections, public health) about the advantages and indications and usage of oral based testing. School nurses with high frequency of interaction.

Use of New Technologies to Maximize the Use of Saliva and Other Fluids (Group D)

Co-Moderators: David C. Duffy, PhD, and William Giannobile, DDS, DMSc

Saliva is a mirror of the body. The composition of saliva and other oral fluids reflect the tissue fluid levels of therapeutic, hormonal, and immunological molecules, as well as the presence of markers for systemic and oral diseases, through viruses, bacteria, and DNA. The analysis of these fluids therefore has great potential in diagnoses in a variety of clinical situations. Techniques that are emerging from a combination of miniaturization technologies and molecular biology will lead to high throughput, automated, portable, low cost, more efficient, and rapid biochemical analyses. Saliva is, in many ways, the ideal bodily fluid for use in these microsystems. The use of this fluid in microsystems has, however, not been exploited to its fullest advantage.

Vision Statement

To develop and utilize new technologies for *in vitro* and *in vivo* monitoring of oral components related to oral and systemic disease. The development of this oral fluid characterization and monitoring will focus on three areas: i) systemic disease diagnosis (e.g., biomarkers for cardiovascular disease and cancer); ii) oral diagnostics (e.g., biomarkers for periodontal disease and dental caries); and iii) drug monitoring (including drug compliance, pharmacokinetics, and pharmacogenomics). The analysis of oral fluid-derived components (cells, DNA/RNA, proteins, hormones, drugs) will be facilitated by the utilization of emerging technologies such as micro- and nano-fabrication, miniaturized analytical systems, microfluidics, microsensors, and high density arrays of DNA.

Goals for the next 5–10 years

- Establish a fundamental understanding of oral fluids (whole saliva, parotid saliva, submandibular saliva, gingival crevicular fluid, minor salivary gland fluid, etc.) using microscopic systems, such as microfluidic systems and microsensors.

- Identify and understand the importance of biomarkers (in oral fluids) in relation to the pathogenesis of oral diseases that can be utilized in miniaturized analytical systems.

- Develop the use of oral fluids as a source for nucleic acids (through shed cells) for genomic analysis (through gene expression analysis, polymorphism and mutation detection) for applications in molecular diagnosis and pharmoacogenomics.

- Investigate interface between collection of samples of oral fluid and micro analytical systems.

- Characterize chemical uniqueness of all oral fluids, i.e., determine what information can be obtained from saliva that cannot be obtained from blood and urine.

- Investigate the role of bioinformatics (e.g., results of high throughput screening) for use in oral diagnostics.
- Develop techniques to measure the microheterogeneity of analytes harvested from specific tooth sites.

- Investigate the use of new, highly sensitive technologies such as mass spectroscopy (e.g., MALDI-TOF) and bioluminescence to improve the sensitivity to proteomic and genomic material in saliva.

- Develop understanding of issues of biocompatibility of oral fluids with materials used in microsystems such as silicon, glass, and polymers.

- Develop methods for rare event detection to increase the range of diseases that can be detected in saliva.

Barriers and Solutions

Regulatory and clinical barriers to *in vitro* and *in vivo* testing:

Barrier: Inadequate training of operators of in vitro diagnostics. *Solution:* Encourage training of dental hygienists, nurses, and physician's assistants.

Barrier: Lack of awareness and acceptance of new technologies by dentists, physicians and third party payers. *Solution:* Improve information dissemination and link treatment outcomes to diagnostic testing.

Barrier: Potential liability issues. *Solution:* Encourage early interaction with FDA, industry and institutional review boards during the development of a technology or product. Address issues through state dental boards.

Barrier: Potential confidentiality and ethical issues arising from the use of these new technologies. *Solution:* Regulation of dissemination of information.

Technological Barriers:

Barrier: Sensitivity to low concentrations of analytes found in saliva. *Solutions*: Improve detection systems, e.g., use of new mass spectroscopy technologies such as MALDI-TOF. Improve sensitivity by developing more sensitive assays, e.g., chemiluminescence and bioluminescence. Develop rare event techniques, e.g., high-speed imaging cytometry.

Barrier: Characterization of integrity of samples, in particular problems of multiple fluid sources, changes in saliva-plasma ratio. *Solution:* Design studies which look to better characterize the dynamics of oral fluids in vitro and in vivo.

Barrier: Biocompatibility of oral fluids with the materials used in microsystems. *Solution:* Develop materials (e.g., polymers) that can be used in microsystems and are compatible with biological fluids. Improve surface modification methods to prevent fouling and blockage of devices by saliva.

Barrier: Cost-effective manufacturing methods for mass-production of microsystems are in an early stage of development. *Solution:* Encourage development of methods and materials that lend themselves to manufacture, e.g., low-cost, non-IC techniques for creating microsystems in polymers and other biocompatible materials.

Scientific Priorities

To develop the use of emerging micro- and nano- technologies in oral fluids diagnostics with particular applications in:

1. systemic disease diagnosis
2. oral disease diagnosis
3. Drug and drug-metabolite monitoring

Implementation strategies

- Need of specific initiatives i.e., RFAs and encouragement of SBIR and STTR applications.
- Partnerships with other NIH institutes and other governmental agencies.
- Establish an NICDR clearinghouse in this specific area.
- Develop a NIDCR web site as a central resource for microsystems and oral based- diagnostics.
- Promote interdisciplinary training programs between dental, medical, biology, chemistry, and engineering groups.
- Promote interdisciplinary symposia involving oral biologists, physicians, physical scientists, and engineering.

List of Workshop Participants

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